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ORIGINAL ARTICLE

Monthly oral ibandronate is effective and well tolerated after 3 years: the MOBILE long-term extension

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Abstract Oral ibandronate is the first bisphosphonate licensed for once-monthly treatment of postmenopausal osteoporosis. The 2-year Monthly Oral iBandronate In LadiEs (MOBILE) registration study assessed bone mineral density (BMD) and markers of bone turnover and showed that monthly oral ibandronate was at least as effective and well tolerated as a 2.5-mg daily oral regimen. In this study, we report the first year of a long-term extension study to MOBILE and a post hoc analysis of patients receiving 3 years of continuous treatment with monthly ibandronate. Patients who completed MOBILE were eligible for the partially randomized, double-blind extension study and received 100 mg (n=359) or 150 mg (n=360) monthly oral ibandronate. A post hoc analysis included patients who received either 100 mg (n=173) or 150 mg (n=169) monthly ibandronate continuously throughout the original 2-year MOBILE study and during the first year of the extension study. After one additional year of treatment (total of 3 years), mean lumbar spine BMD increased a further 1.5 and 1.1% in the 150 and 100 mg arms, respectively, compared with 2-year data (original MOBILE study). Total hip BMD changed by 0.3 and −0.08%, respectively. In the post hoc analysis, 3-year increases in lumbar spine BMD were significant in patients receiving ibandronate 150 mg monthly (7.6%; p<0.0001 vs. baseline) and 100 mg monthly (6.4%; p<0.0001 vs. baseline). Both groups achieved significant increases in total hip BMD after 3 years compared with baseline (3.4%, 100 mg; 4.1%, 150 mg; p<0.0001). Serum C-telopeptide of the alpha chain of type I collagen decreased significantly over 3 years' treatment (p<0.001; all comparisons vs. baseline), remaining within the premenopausal range. Once-monthly oral ibandronate was well tolerated with a low incidence of clinical osteoporotic fractures and upper gastrointestinal events. In conclusion, 150-mg monthly oral ibandronate is an effective and well-tolerated long-term treatment for postmenopausal osteoporosis, with consistent improvement in BMD and bone turnover during 3 years' continuous treatment.

Keywords Bone mineral density · Bone turnover · Ibandronate · Monthly · Serum CTX

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Introduction

Oral ibandronate is the first once-monthly oral bisphosphonate to be licensed for the treatment of postmenopausal osteoporosis [1]. Gains in bone mineral density (BMD) and

reductions in biochemical markers of bone turnover have been shown to correlate with reduction in vertebral [2] and non-vertebral fracture risk [3], and these parameters were assessed in the 2-year Monthly Oral iBandronate In LadiEs (MOBILE) study [4, 5]. Results showed that the once-monthly oral ibandronate regimens (50 mg on two consecutive days [50+50 mg], 100 mg, or 150 mg) were at least as effective as a 2.5-mg daily oral ibandronate dose in increasing BMD and reducing markers of bone turnover [4, 5]. In fact, during 2 years of treatment, ibandronate 150-mg monthly achieved statistically superior increases in lumbar spine and total hip BMD compared with the 2.5-mg daily arm ($p<0.05$). In addition, pronounced decreases in bone resorption into the normal premenopausal range [6] were observed in all arms at the time of first assessment (3 months), and these were maintained throughout the 2-year study. The 2.5-mg daily oral regimen has previously demonstrated significant vertebral fracture risk reduction versus placebo (relative risk reduction 62%; $p=0.0001$; oral iBandronate Osteoporosis vertebral fracture trial in North America and Europe (BONE) study) and non-vertebral fracture risk reduction in a post hoc subgroup analysis (relative risk reduction 69% in patients with a baseline femoral neck BMD *T*-score<−3; $p=0.012$) [7]. Monthly oral ibandronate 150 mg was also as well tolerated as the daily regimen, which has been shown to have a tolerability profile similar to placebo, and was consequently approved for the treatment of women with postmenopausal osteoporosis [7]. In this study, we present data from a preplanned 1-year interim analysis of a long-term extension to the MOBILE study, designed to provide additional data on the long-term efficacy and tolerability of monthly oral ibandronate.

Materials and methods

Study design and participants

This multinational, multicenter, partially randomized, double-blind extension study was conducted in 31 of the 65 centers participating in the original MOBILE study. Participants were women with postmenopausal osteoporosis who had completed 2 years of the randomized, double-blind MOBILE study with at least 75% compliance with the monthly regimen (either active treatment or placebo tablets to maintain blinding). Inclusion and exclusion criteria for MOBILE have been published previously [4].

Eligible patients were allocated to one of two treatment groups for the long-term extension. Patients who received ibandronate 100 or 150 mg monthly in MOBILE continued on the same dose in the extension study, whereas those who had previously received 2.5 mg daily or 50+50 mg monthly were re-randomized either to 100 or 150 mg monthly. To maintain double-blind conditions, all patients took placebo matching the alternative tablet with their active medication. Patients also received vitamin D 400 IU a day and elemental calcium of at least 500 mg a day (upper limit 1,500 mg a day).

Assessments

The primary efficacy variable of the MOBILE long-term extension is the relative change (%) in mean lumbar spine (L2–L4) BMD at 36 months from the end of the 2-year MOBILE study, with interim analyses being carried out at the 12- and 24-month timepoints of the long-term extension. In addition, the secondary efficacy variables are relative change (%) at 12, 24, and 36 months in total hip BMD and the marker of bone resorption serum C-telopeptide of the alpha chain of type I collagen (sCTX) at trough (pre-dose) and at peak suppression (at steady state, that is, 7 days after study drug administration), both in a subpopulation of 150 patients from selected centers. In the original 2-year MOBILE study, trough samples were collected at baseline and months 3, 6, 12, and 24.

Adverse events were monitored throughout the study and graded by severity and relationship to treatment.

Statistical analysis

The primary analysis population for all efficacy endpoints was the intent-to-treat (ITT) population, and analyses were also performed on the per-protocol (PP) population. The safety population comprised all patients who received at least one dose of study medication and at least one safety follow-up.

The primary and secondary efficacy data, and the safety data, were re-analyzed in a post hoc analysis, which included only those patients who had received 100 or 150 mg monthly oral ibandronate continuously for 3 years (i.e., for 2 years in MOBILE and then a further 1 year in the long-term extension) and excluded patients who had switched from the daily or 50+50 mg regimen at the start of the extension study.

Results

Patient disposition and baseline characteristics

Of the 65 centers participating in the original MOBILE study, 31 centers elected to participate in the long-term extension. Of 1,291 patients who completed the MOBILE study, 719 continued into the long-term extension study (100 mg: $n=359$; 150 mg: $n=360$; Fig. 1). Baseline patient characteristics for the ITT population were well balanced

Fig. 1 Patient disposition

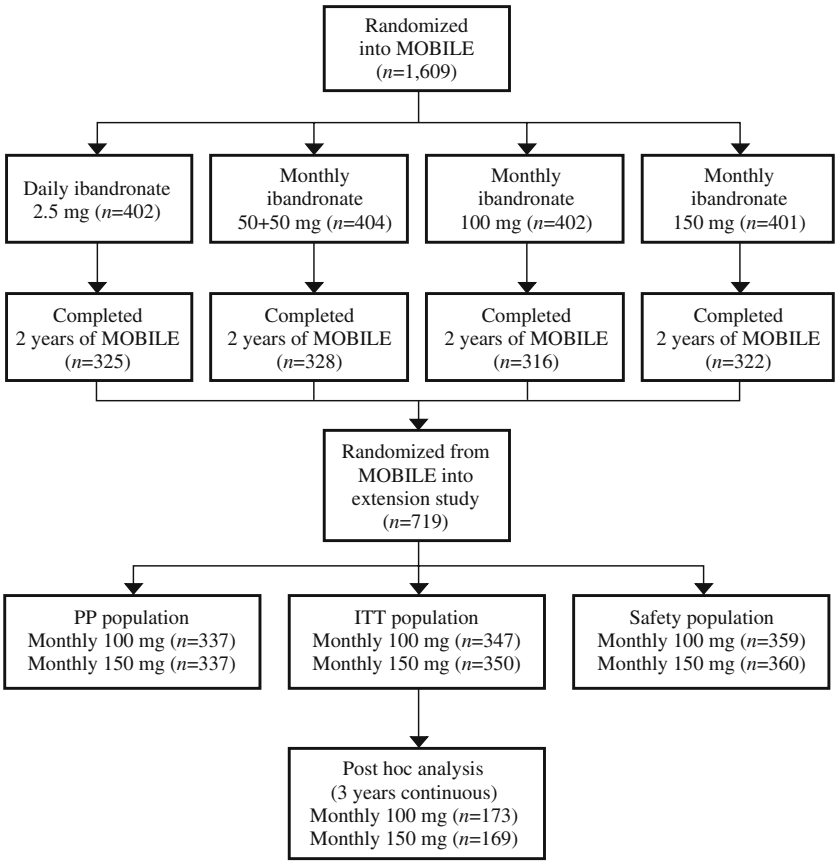

Table 1 Baseline demographics of patients entering the MOBILE study long-term extension

	Ibandronate 100 mg monthly (n=347)	Ibandronate 150 mg monthly (n=350)
Age (years)	67.6	67.6
Weight (kg)	64.6	64.6
Height (cm)	158.0	157.8
Body mass index (kg/m^2)	25.9	26.0
Lumbar spine (L2–L4) BMD (g/cm^2)	0.79	0.80[a]
Lumbar spine (L2–L4) BMD (T-score)	−2.92	−2.90[a]
Total hip BMD (g/cm^2)	0.77	0.79[a]
Total hip BMD (*T*-score)	−1.63	−1.49[a]
Serum CTX (ng/ml)[b]	0.20	0.18

[a] n=349

[b] Baseline sCTX levels are the re-analyzed results from the MOBILE 2-year samples (n=56 and 68 for 100- and 150-mg arms, respectively). Median values presented.

across treatment arms (Table 1). The additional year of ibandronate treatment was completed by 96% of patients (n=344 in each arm).

The post hoc analysis included 173 and 169 women (168 for lumbar spine) in the 100 mg and 150 mg groups, respectively, who received the same ibandronate dose (100 or 150 mg) throughout the 2 years of MOBILE and the first year of the long-term extension.

Efficacy analysis

All patients completing 1 year of the long-term extension - After 1 year of treatment in the extension study, mean additional increases in BMD from the MOBILE 2-year results in the 150 mg arm were 1.5 and 0.3% for the lumbar spine and total hip, respectively (ITT population). In the 100 mg arm, mean lumbar spine BMD increased by an extra 1.1%, and total hip BMD remained almost constant (−0.08%).

In the ITT population, median peak sCTX (measured 6 days after month 6 dosing in the extension) decreased from the MOBILE 2-year values by 42.3 and 31.3%, respectively, in the 150- and 100-mg arms. Median trough sCTX (measured

before month 12 dose) increased by 10.3 and 22.2%, respectively (from MOBILE 2-year values). sCTX levels remained within the premenopausal range [6], and similar results were obtained in the PP analysis (data not shown).

Patients included in the post hoc analysis The post hoc analysis (ITT population) showed that lumbar spine BMD increased consistently over 3 years of continuous treatment with monthly oral ibandronate (Fig. 2). After 3 years of treatment, an increase of 7.6% was observed in the 150-mg monthly arm ($p<0.0001$ vs. baseline), and the additional BMD increase from year 2 to year 3 (1.2%) was also highly significant ($p<0.0001$). In the 100-mg monthly arm, a 6.4% increase in lumbar spine BMD was observed over 3 years ($p<0.0001$), and there was a significant increase of 0.9% ($p=0.003$) from year 2 to year 3. Similarly, the analysis of mean relative BMD changes for the total hip showed consistent and significant increases over the 3 years in the 150-mg (4.1%) and 100-mg (3.4%) arms compared with MOBILE baseline values ($p<0.0001$; Fig. 3). Femoral neck and trochanter BMD gains were 3.5 and 6.2% for the 150-mg arm, respectively, and 2.5 and 5.4% for the 100-mg arm, respectively. From year 2 to year 3, mean femoral neck and trochanter BMD (analysis not predefined) increased by an additional 0.4 and 0.6%, respectively, in the 150-mg group, with changes of 0.0 and 0.4%, respectively, in the 100-mg group (ITT population). Results were confirmed in the analysis of the PP population (data not shown). All doses showed consistent and statistically significant increases compared with MOBILE baseline values ($p<0.0001$ for all comparisons).

With 3 years of continuous treatment with 150 and 100 mg monthly ibandronate, median sCTX (peak suppression level, 6 days after month 30 dose) decreased by 83.3 and 70.1%, respectively ($p<0.0001$ vs. baseline for both comparisons), and median trough sCTX (before month 36 dose) by 64.9 and 52.0% ($p<0.0001$ and $p=0.0003$ vs. baseline, respectively). All sCTX levels remained within the normal premenopausal range (Fig. 4) [6]. Analyses in the PP population provided similar results to the ITT population for all efficacy analyses in the post hoc subgroup (data not shown).

Safety analysis

All patients completing 1 year of the long-term extension - Monthly oral ibandronate was well tolerated, with a similar number of adverse events occurring in the 150-mg ($n=360$) and 100-mg ($n=359$) treatment arms. Overall, at least one adverse event was experienced by 53% of patients in the 150-mg arm and by 56% in the 100-mg arm. Importantly, the incidence of clinical osteoporotic fractures was low (150 mg: 2.2%; 100 mg: 3.6%), as was the incidence of upper gastrointestinal (GI) disorders (150 mg: 6.9%; 100 mg: 4.5%). The incidence of drug-related adverse events leading to withdrawal was similarly low across treatment groups (150 mg: 0.3%; 100 mg: 0%). Serious adverse events, reported during the 1-year extension period, were infrequent (150 mg: 7.5%; $n=27$; 100 mg: 7.8%; $n=28$), and only one was considered by the investigator to be possibly related to treatment (chest pain in the 150-mg arm). No serious upper GI disorders were reported in either treatment arm. One death (pancreatic cancer) occurred during the long-term extension and was considered by the investigator to be unrelated to study treatment.

Patients included in the post hoc analysis The overall incidence of upper GI adverse events was analyzed in those patients receiving 3 years of continuous treatment with monthly ibandronate. The incidence was low, with upper GI adverse events occurring in 15 (8.5%) and 8 (4.5%) patients, respectively, in the 150- and 100-mg groups. Only two patients (1.1%) in the 150-mg group and one patient (0.6%) in the 100-mg group withdrew as the result of an

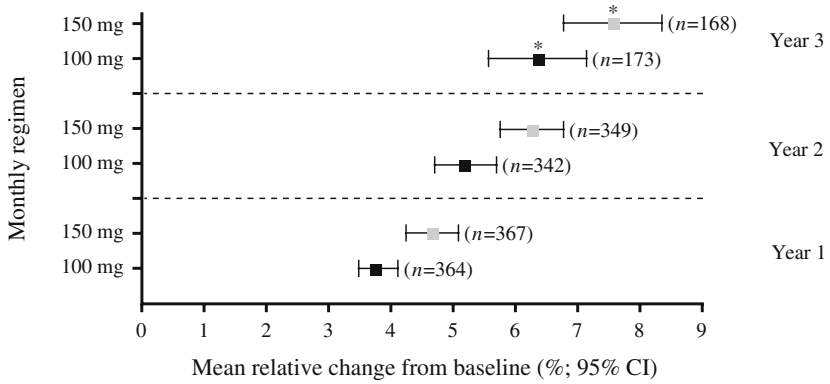

Fig. 2 Mean relative change (%) from baseline in lumbar spine BMD with 3 years of continuous treatment with monthly ibandronate (ITT population; combined post hoc BMD analysis)

*$p<0.0001$ vs baseline
Data presented from MOBILE (years 1 and 2) and for patients randomized to 150 mg and 100 mg groups in MOBILE and who then continued on this treatment in year 3

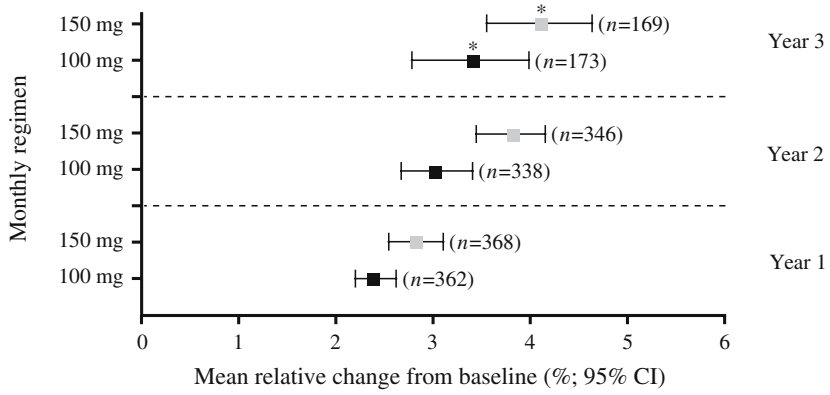

Fig. 3 Mean relative change (%) from baseline in total hip BMD with 3 years of continuous treatment with monthly ibandronate (ITT population; combined post hoc BMD analysis)

*p<0.0001 vs baseline
Data presented from MOBILE (years 1 and 2) and for patients randomized to 150 mg and 100 mg groups in MOBILE and who then continued on this treatment in year 3

upper GI adverse event. No serious upper GI adverse events were reported in this population.

Discussion

In the original MOBILE study, 1 and 2 years of treatment with 150 mg monthly oral ibandronate produced significant increases in lumbar spine and proximal femur BMD compared with the 2.5-mg daily oral regimen [4, 5]. In the long-term extension to MOBILE, further increases in lumbar spine and proximal femur BMD were achieved in patients receiving an additional year of 150 mg monthly ibandronate. Notably, the additional increases in lumbar spine and proximal femur BMD from year 2 to year 3 were significant (p<0.0001). Moreover, lumbar spine and total hip BMD increased progressively in those patients receiving 3 years of continuous treatment with 150 mg monthly ibandronate. It should be noted, however, that the published data from MOBILE years 1 and 2 [4, 5] are based on the PP population and are not therefore directly comparable with the MOBILE extension study data presented here that are based on the ITT population.

sCTX levels remained within the premenopausal range for patients completing 1 year of the long-term extension and for those in the post hoc analysis. Overall, patients had a high level of suppression relative to the core study baseline after 3 years of continuous treatment.

Long-term treatment was well tolerated during 3 years of continuous treatment with 150 mg monthly ibandronate. No instance of osteonecrosis of the jaw was reported. In patients receiving 3 years of continuous treatment, there were no serious upper GI events reported, and only three patients in total withdrew for upper GI events.

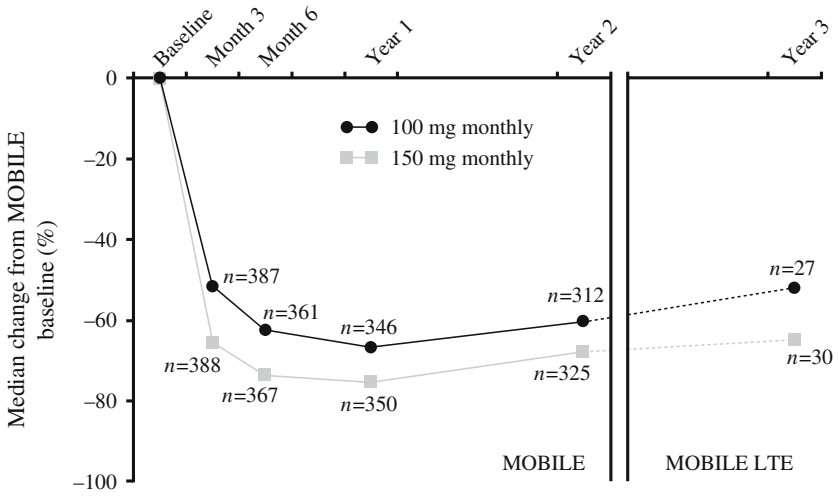

Fig. 4 Median change from baseline in trough serum CTX (ITT population; post hoc analysis; *LTE* long-term extension)

ITT population
Dotted lines represent time intervals where additional measurements might have shown fluctuations in serum CTX
The gap represents that a time interval between the core and LTE studies could occur
Serum CTX was only assessed at selected centers in the long-term extension

In addition, improved adherence to therapy has been previously reported with the monthly ibandronate dosing regimen. In the UK PERSIST study there was a 47% relative improvement in the proportion of patients persisting at 6 months with a monthly oral ibandronate regimen (plus a patient support program) versus a weekly oral alendronate regimen [8]. In a US claims database retrospective study, patients receiving monthly ibandronate were 31% more likely to persist with therapy at 9 months compared with those receiving weekly bisphosphonate therapy ($p<0.0001$) [9].

The long-term duration and the large patient population analyzed, including the 342 patients who were followed during three continuous years of treatment with a single monthly ibandronate dose, contribute to the strengths of this analysis. The study is limited by the lack of a placebo group, but long-term treatment with placebo in postmenopausal women with osteoporosis would be unethical, and thus the 100-mg group was included as a lower dose comparator.

In conclusion, once-monthly oral ibandronate is an effective and well-tolerated treatment for postmenopausal osteoporosis, with sustained efficacy after 3 years of continuous treatment. Monthly oral ibandronate continues to increase BMD and reduce markers of bone turnover, which are key factors contributing to increased bone strength. Due to its convenience and favorable tolerability profile, monthly oral ibandronate improves long-term adherence, as reported previously, and therapeutic outcomes.

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